American Journal of Medical Genetics 68:82–85 (1997)

Brief Clinical Report

Lethal Multiple Pterygium Syndrome: Suggestion for a Consistent Pathological Workup and Review of Reported Cases

Ursula G. Froster,[1]* Thomas Stallmach,[2] Josef Wisser,[1] Gundula Hebisch,[1] Mario B. Robbiani,[1] Renate Huch,[1] and Albert Huch[1]

[1]*Clinic of Obstetrics, Department of Obstetrics and Gynecology, University Hospital Zurich, Zurich, Switzerland*
[2]*Institute of Clinical Pathology, Department of Pathology, University Hospital Zurich, Zurich, Switzerland*

We report on 2 brothers with lethal multiple pterygium syndrome (LMPS) born to nonconsanguineous parents as late spontaneous abortions. Both fetuses presented with massive nuchal edema, and facial anomalies including cleft palate and broad ribs. Apparently, several subgroups of LMPS exist. Differentiation is difficult, as there is no consistent agreement on a workup protocol for autopsies. We compared the findings in the literature on cases with LMPS, and we suggest a standardized workup as an initial step for more efficient differentiation between various subgroups. Am. J. Med. Genet. 68:82–85, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: lethal multiple pterygium syndrome; nuchal edema; cleft palate

INTRODUCTION

Lethal pterygium syndromes (LMPS) present prenatally with hydrops, nuchal edema, multiple webs across major joints, and intrauterine death in the second or early third trimester of pregnancy. The cause of LMPS is unclear. Inheritance is either autosomal or X-linked recessive. Clinical differentiation of separate entities is difficult. Bone fusions and additional malformations may be useful criteria in distinguishing various subgroups. Autopsy studies in the published cases are inconsistent, and standard procedures are not always used. This leads to a lack of essential information of morphological changes. So far, it is almost impossible to differentiate single entities within the group of lethal multiple pterygium syndromes (LMPS).

We report on a family with 2 affected male fetuses displaying LMPS. Comparison of the findings with the latest review by de Die-Smulders et al. [1990], and additional reports on this condition (Table I), led us to suggest a standardized workup with special reference to aspects of pathogenesis of cases with LMPS, as far as this is possible in macerated fetuses.

CLINICAL REPORTS

Patient 1

The fetus was the product of the first pregnancy to a 32-year-old woman and her 30-year-old husband. The parents were nonconsanguineous.

The first clinical and utrasonographic study in week 17 of gestation was reported as normal. At 20 gestational weeks, ultrasonography showed a malformed fetus with microcephaly, enlarged ventricles, hydrops, hydrothorax, ascites, ahydramnios, and multiple amniotic cysts. The pregnancy ended with an intrauterine death at 24 weeks of gestation. In this macerated fetus, the diagnosis of nuchal edema was not further differentiated and LMPS had not been considered. Hence, a low recurrence risk was given to the parents.

At autopsy, the 24-cm-long autolytic fetus had a microcephalic and dolichocephalic skull, massive nuchal edema of 12 cm diameter, and a median cleft palate. External genitalia were undifferentiated, and internal genitalia were male. Karyotype analysis failed.

Patient 2

The pregnancy with the index-patient was the second pregnancy to this couple. It was remarkable as there was fetal hydrops at 13 + 4 weeks gestation, which increased. There were no fetal movements, neither on ultrasound nor recognized by the mother. Fetal hydrops with massive neck edema of 6.2 × 3.9 cm diameter and generalized hydrops were seen on ultrasound (Fig. 1a). Karyotype analysis from amniocytes showed normal male, 46, XY.

Contract grant sponsor: the Deutsche Forschungsgemeinschaft; Contract grant number: Fr 653/13-1

*Correspondence to: Prof. Dr. med. Ursula Froster, Klinik und Poliklinik für Geburtshilfe, Departement Frauenheilkunde, Universitätsspital Zürich, Frauenklinikstr. 10, CH-8091 Zürich, Switzerland.

Received 29 January 1996; Accepted 22 April 1996

TABLE I. Anomalies in Addition to Nuchal Edema, Generalized Hydrops, and Congenital Webbing Across Major Joints in Cases With LMPS*

Additional findings	de Die-Smulders et al., 1990	Clementi et al., 1995	Spearitt et al., 1993	Moerman et al., 1990	Case 1	Case 2	Total
Hypertelorism	20/21		+	+	+	+	27/28
Antimongloid slant of palpebral fissures	13/17		+	+	+	+	20/24
Flat nose	22/23		+	−	+	+	25/30
Cleft palate	15/21		+	3/4	+	+	21/28
Micrognathia	25/25	+	+	3/4	+	+	32/33
Apparently low-set ears	21/22		+	3/4	+	+	27/29
Lung hypoplasia	22/25		+	4/4	+	+	29/32
Cardiac hypoplasia	9/16		+		+	+	12/19
Scoliosis	5		−	−		+	6
Diaphragmatic hernia thin diaphragm	4		+	−	−	−	5
Vertebral defects	7/13	−	−	−		+	8/20
Vertebral fusion	5/15	−	−	−		+	6/22
Hypoplastic ilia	5/10	+	−	−		+	7/17
Rib hypoplasia	7/15	−	−	−		−	7/22
Broad or spatulated ribs	4/8	−	−	−		+	5/15
Hypoplastic scapula	7/12	+	−	−		+	9/19
Undermodelling of long bones	12/16	+	−	4/4		+	18/23
Proximal radio-ulnar fusion	3/10		−	−		−	3/16
Hip dislocation	3/7	−	−	−		−	3/14
Placental anomalies	5		−	4/4	+	+	11

* Table summarizes published data, including review by de Die-Smulders et al. [1990], and presently described cases. If only one case was described in detail, as in Spearitt et al. [1993] and Clementi et al. [1995], this was counted as one, while in Moerman et al. [1990], all 4 cases were described in more detail, and all 4 cases were counted. "Total" gives the number of cases in which this anomaly was found and the total of cases in which it was looked for. Congenital webbing across major joints, nuchal edema, and generalized hydrops were constant findings in these cases. Therefore, they are not tabulated here. There were no distinguishing anomalies in either sex. Numbers show cases investigated vs. positive findings; blank spaces mean not done.

Death occurred at 24 gestational weeks of intrauterine life. Expulsion of the fetus was induced by prostaglandines.

At autopsy, the male fetus weighed 560 g, with a length of 26 cm (appropriate for 20 gestational weeks). The nuchal edema was septated, reaching from the head to the caudal end of the spine, measuring 9.5 × 9 cm. There were multiple pterygia extending across the axillae to the thorax, from the neck to the chest, antecubital, inguinal, and popliteal, containing the popliteal nerve (Fig. 1b, c). The skeletal muscle was only rudimentary (Fig. 1g). No information is available on motor cells because of the advanced autolytic process. There was fusion of the cervical spine 3–8, and a left-sided scoliosis of the spine, but no synostosis of the radius and ulna at the elbow joints (Fig. 1d–f). The heart and lungs were hypoplastic with a weight of 0.56 g (<5th centile), appropriate for week 16 of gestation. The lung weighed 1.72 g (<5th centile), appropriate for week 15 of gestation. The diaphragm was thin. Fetal X-ray studies showed fusion of the cervical spine C3–7 and a left-sided scoliosis (Fig. 1e).

The face was remarkable as there was hypertelorism with downslant of the palpebral fissures, a flat nose, and a median cleft palate. The placenta was of normal weight for gestational age and showed hydropic villi and calcification of the basal membrane.

DISCUSSION

Lethal multiple pterygium syndrome (LMPS) is defined as a recessive or X-linked disorder. The syndrome is characterized by fetal hypokinesia, joint contractures, pterygia, and intrauterine death. Cystic hygroma and hydrops are frequently associated [de Die-Smulders et al., 1990], and this group of disorders represents one of the main differential diagnoses of fetal hydrops, especially if it recurs in consecutive pregnancies.

The pathogenesis of LMPS is unknown. Primary aplasia of developing muscle fibres [Moerman et al., 1990] and abnormally fragile collagen [Hartwig et al., 1989] have been suggested as possible pathogenetic mechanisms. Other suggested mechanisms include fetal a/hypokinesia and fetal edema [Hall, 1984]. In the fetuses reported here, muscle hypoplasia was severe, which supports an early-onset fetal myopathy as the underlying mechanism.

At present, there are two classifications suggested for a differential diagnosis of LMPS. The classification by Hall [1984] is based on clinical findings, the onset of intrauterine growth retardation, and the timing and extent of neck swelling, as well as the presence or absence of bony fusions and errors of bone modelling. The classification suggested by de Die-Smulders et al. [1990] distinguishes between three groups, the early type, the late type, and the Finnish type [Herva et al., 1985], which has specific neuropathological changes with a loss of axons in the ventral and lateral columns of the spinal cord, with subtotal loss of the anterior horn motor neurons at brain-stem level. Neurological findings in surviving cases with LMPS are only reported in

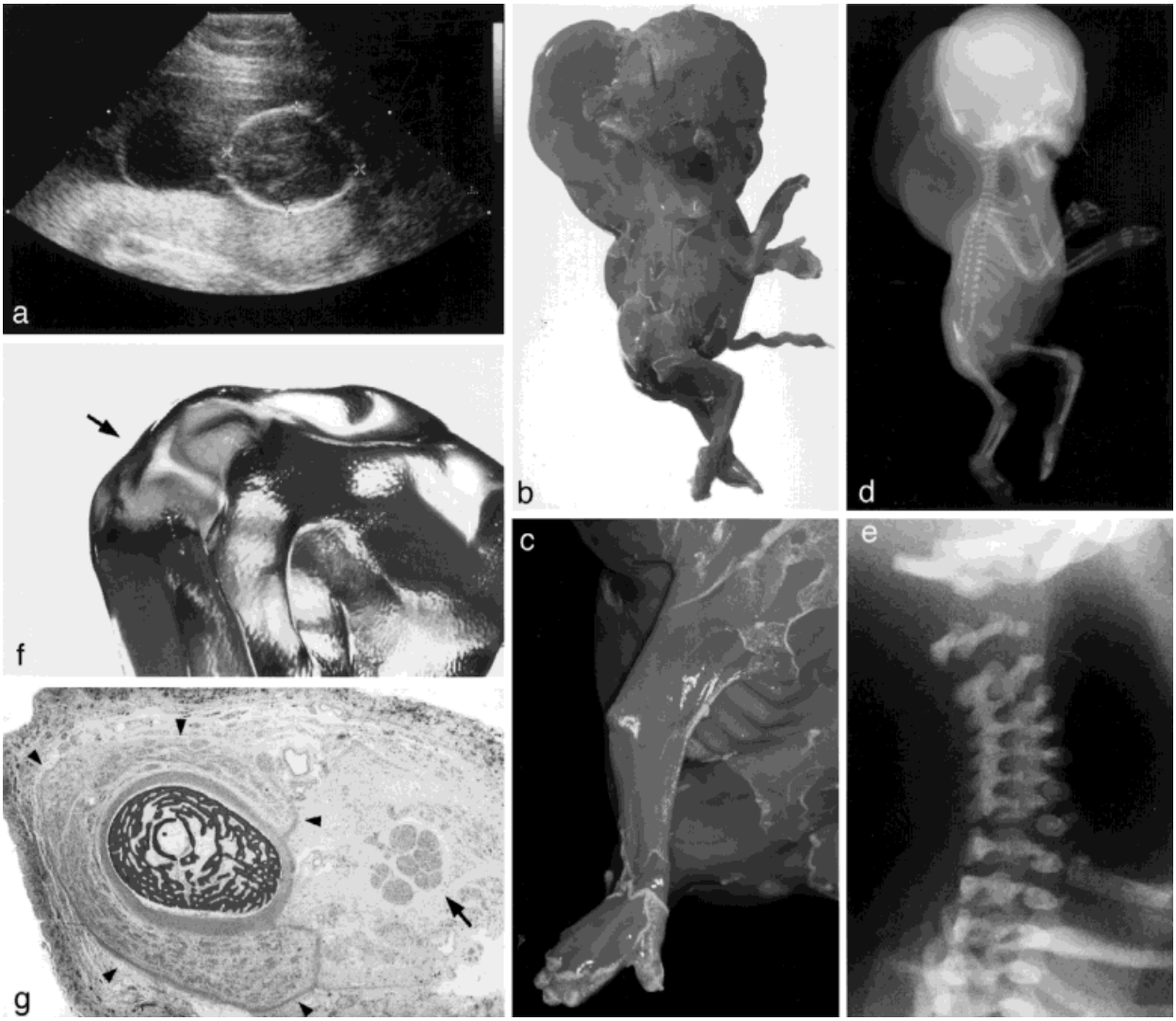

Fig. 1. **a**: Ultrasonography of fetal head, showing massive nuchal edema. **b**: Severely macerated stillborn fetus with hygroma colli, extending to lower thoracic spine, and with downslanting palpebral fissures and antecubital webs. **c**: All major joints are not freely mobile: detail from right elbow. **d**: X-ray examination does not show anomalies of limbs. Ribs appear unusually broad. There is bony fusion in part of the vertebral column. **e**: Detail from X-ray of cervical spine demonstrates bony fusion of vertebrae 3–7. **f**: Limbs were made translucent and cartilage was stained by alizarian blue. Hence all interarticular spaces could be examined for possible fusion of cartilage, which would not have been visible by X-ray examination. Arrow indicates interarticular space of a knee joint. **g**: Transverse section of thigh: all limbs are slim due to hypoplastic muscles. Bone in the center is of normal size; adjacent quadriceps muscle consists of a few very small muscle fibers. Outline of muscle compartment is indicated by arrowheads. Skeletal muscle is rudimentary. Ischial nerve is of normal size (arrow); surrounding muscle tissue is extremely hypoplastic.

single cases and may not be consistent. The Finnish type is considered a specific entity characterized by multiple contractures without cystic hygroma. In some respect it resembles Pena Shokeir I syndrome, but differs in length of survival time and presence of hydrops.

The cases reported by Tolmie et al. [1987] follow an X-linked pattern of inheritance. The main distinguishing features are broad ribs and clavicles, which were also present in our cases, suggesting that our cases might present the X-linked type of LMPS. Following the subgroups of de Die-Smulders et al. [1990], our cases might best be compatible with their early-onset form, while following the classification of Hall [1984], the group of LMPS with bony fusion would be that to which our cases might belong.

Comparing symptoms in different cases of LMPS (Table I), it becomes evident that there is almost no consistency in reporting clinical findings and in the postmortem workup. However, this is essential in order to distinguish between subgroups or to establish whether

there is a distinguishable X-linked type of LMPS. Thus, we suggest the following protocols in case of a fetus with LMPS:

1. External documentation, including extension of webbing, extension of edema, facial anomalies (micrognathia, gaping mouth, position of ears and palpebral fissures, cleft palate), and anomalies of the external genitalia.
2. X-rays to document fusion of the cervical spine or vertebral elements are essential. Some of the more subtle changes, which were discussed as possible distinguishing traits, are cartilagenous or bony fusions. In fetuses these may be seen on X-rays, but might be better documented by alizarian blue staining.
3. Autopsy should document size of the heart and possible heart defects, but also the quality of the diaphragm, since there have been some cases with a thin diaphragm or even diaphragmatic hernia, which might be an expression of general muscle involvement. Even in cases with severe autolytic changes it is possible to register the striking lack and degeneration of muscle fibers.
4. Neurohistological investigations may be hampered by degree of autolysis; however, an attempt should be made to exclude major anomalies, especially anterior horn-cell loss and hypoplasia of various areas of the brain.
5. Documentation by good photography.
6. Cytogenetic studies.

For the ultrasonographer, cases with LMPS need to be differentiated from other cases with nuchal web as the main presenting sign.

One subgroup within nuchal web cases can be distinguished through normal chromosomal results. Even though the diagnosis of LMPS separates another subgroup of conditions from the category of "nuchal web" cases, we are still not able to distinguish one or more well-defined and pathogenetically easy-to-distinguish specific syndrome(s). On the basis of the additional findings summarized in Table I, it seems that helpful differential diagnostic criteria for LMPS might be skeletal anomalies, movement patterns, and thin, hypoplastic muscles. However, the most important point is that in all fetuses with nuchal edema, a detailed autopsy should be made available for future genetic counselling purposes and for a more specific differential diagnosis.

ACKNOWLEDGMENTS

We are grateful to Ms. B. Benz for technical assistance in the documentation of cases. We thank Prof. Albert Schinzel, Institute of Human Genetics and Prof. J. Briner, Institute of Clinical Pathology, University of Zürich, Zürich, for helpful comments and discussion. U.G.F. was supported by a grant from the Deutsche Forschungsgemeinschaft (Fr 653/13-1).

REFERENCES

Clementi M, Notari L, Tenconi R (1995): Lethal multiple pterygium syndrome: Importance of fetal physical examination. Am J Med Genet 57:119–120.

de Die-Smulders CEM, Schrader-Stumpel CTRM, Fryns JP (1990): The lethal multiple pterygium syndrome: A nosological approach. Genet Counselling 1:12–23.

Hall JG (1984): Editorial comment: The lethal multiple pterygium syndromes. Am J Med Genet 17:803–807.

Hartwig NG, Vermeij-Keers C, Bruijn JA, van Groningen K, Ottervanger HP, Holm JP (1989): Case of lethal multiple pterygium syndrome with special reference to the origin of pterygia. Am J Med Genet 33:537–541.

Herva R, Leisti J, Kirkinen P, Seppänen U (1985): A lethal autosomal recessive syndrome of multiple congenital contractures. Am J Med Genet 20:431–439.

Moerman P, Fryns JP, Cornelis A, Bergmans G, Vandenberghe K, Lauweryns JM (1990): Pathogenesis of the lethal multiple pterygium syndrome. Am J Med Genet 35:415–421.

Spearitt DJ, Tannenberg AEG, Payton DJ (1993): Lethal multiple pterygium syndrome: Report of a case with neurological anomalies. Am J Med Genet 47:45–49.

Tolmie JL, Patrick A, Yates JRW (1987): A lethal multiple pterygium syndrome with apparent X-linked recessive inheritance. Am J Med Genet 27:913–919.